Role of the WW Domain in Signaling and Disease

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The WW domain is a protein-protein interaction module composed of 35-40 amino acids. It is the smallest, monomeric, triple-stranded, anti-parallel beta-sheet protein domain that is stable in the absence of disulfide bonds, cofactors or ligands. The major features of the WW domain primary structure are: (i) two conserved trytophans (W) spaced 20-22 amino acids apart; (ii) a block of two or three aromatic amino acids located centrally between the two signature tryptophans, and (iii) a conserved proline located three amino acids carboxyterminal to the second conserved tryptophan. The WW domain binds proline-rich ligands. Based on the ligand binding specificity, the WW domain can be divided into five groups. One of the groups represented by the Pin1WW domain has recently been shown to function as a phosphoserine- or phosphothreonine-binding module. Shortly after its delineation, the WW domain has become a subject of general interest because several signaling complexes that the domain mediates have been implicated in human diseases including Alzheimer's Disease and Muscular Dystrophy.

We have shown that the WW domain of dystrophin forms a complex with beta dystroglycan and that the domain is crucial in maintaining the integrity of the Dystrophin Glycoprotein Complex. Crystal structure of the dystrophin fragment in complex with the carboxyterminal tail of beta dystroglycan illuminated molecular details of this complex and revealed cooperation of the WW domain with EF hands. Mapping of naturally occurring point mutations on the WW domain structure and evaluation of these mutations in animal models for dystrophic phenotype are in progress.

We have shown that the processing of Alzheimer's Amyloid Precursor Protein (APP) is affected by three adapter proteins that interact with the carboxyterminal tail of APP. One of the adapter proteins, termed FE65 harbors a WW domain. The FE65 WW domain recognizes 5 protein species in brain cell lysates, two of which are isoforms of Mena, a protein that regulates cytoskeletal dynamics. We have shown that overexpression of FE65 in cell culture stimulates beta-Amyloid peptide production, whereas the FE65 with the mutated WW domain abrogates this process. We have focused our research on the identification of all ligands to the WW domain of FE65 and on the mechanism by which FE65 regulates APP biology.

In sum, we have identified a small module that mediates protein-protein interaction and that provides us with a molecular tool for dissection of signaling pathways, for diagnosis of certain genetic diseases and eventually for therapeutic interventions.